

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

Manne Satyanarayana REDDY et al.

Art Unit: 1625

Application No.: 10/647,449

Examiner: C. C. Chang

Filed: August 25, 2003

For: POLYMORPHIC FORMS OF (S)-REPAGLINIDE AND
THE PROCESSES FOR PREPARATION THEREOF

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

SUPPLEMENTAL REPLY BRIEF

This paper is submitted in response to the Supplemental Examiner's Answer that was mailed on February 26, 2007 for the above-identified application. Submission of a response to the Supplemental Examiner's Answer is due by April 26, 2007. Accordingly, this paper is being timely filed.

1. **Status of the Claims**

Claims 1-57 were finally rejected in an Office Action mailed on March 6, 2006, although claims 3, 39, 49, 52 and 55 were previously cancelled in an amendment submitted on December 1, 2005. The Examiner acknowledged in the Examiner's Answer that claims 3, 49, 52 and 55 had been cancelled. The Examiner now acknowledged in the Supplemental Examiner's Answer that claim 39 had been cancelled. Accordingly, claims 1-2, 4-38, 40-48, 50, 51, 53, 54, 56 and 57 are the subject of this appeal.

2. Grounds of Rejection to be Reviewed on Appeal

A. Whether claims 38 and 40-48 are anticipated under 35 U.S.C. § 102(b) by Grell et al (U.S. Patent No. 5,312,924; "Grell I").

B. Whether claims 1, 34 and 35 are anticipated under 35 U.S.C. § 102(b) by Grell I.

C. Whether claims 1, 2, 4-37, 50, 51, 53, 54, 56 and 57 are rendered unpatentable under 35 U.S.C. § 103(a) by Grell I in view of Grell et al. (*J. Med. Chem.*, 1998, 41:5219-5246; "Grell II") and Brittain, ed. (Polymorphism in Pharmaceutical Sciences, 1999, pp. 179-79, 185, 219; "Brittain").

D. Whether claims 8-18 are invalid under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description and enablement requirements.

3. Argument

The following discussion is directed to arguments and statements that were presented in the Supplemental Examiner's Answer.

A. Rejection of Claims 38 and 40-48 Under 35 U.S.C. § 102(b)

Claims 38 and 40-48 stand finally rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Grell I. Claims 38 and 40-48 are directed to amorphous (S)-repaglanide and a process for its manufacture. The Examiner stated in the Supplemental Examiner's Answer that the evaporation residue of col. 90, lines 5-6, is amorphous S-repaglanide as claimed. According to the Examiner, were the residue a crystal, it would have been described as "the crystal is recrystallised in ethanol/water."

Appellants maintain that the Examiner has not provided any evidence or scientific reasoning to establish that the evaporation product of Grell I is amorphous (S)-repaglanide, or amorphous (S)-repaglanide having an X-ray powder diffraction pattern substantially as shown in Figure 4 of the instant specification. Further, the two additional references provided in the Examiner's Answer: Bernstein, "Polymorphism in Molecular Crystals," p. 254 (2002) ("Bernstein"); and Ronsen et al. (U.S. Patent No. 5,672,612; "Ronsen"); do not supply the extrinsic evidence necessary to support the

rejection. In fact, Bernstein and Ronstein support Appellants' position that the Examiner has failed to make out a *prima facie* case of anticipation.

Although Bernstein does state that amorphous pharmaceutical material may be obtained by "removal of solvent," Bernstein goes on to state in the same sentence that such removal of solvent is from a solvate, which point the Examiner failed to include in the Examiner's Answer. Nowhere does Grell I disclose, or even suggest, that the (S)-repaglinide is a solvate or hydrate. The Examiner's reliance on Bernstein merely adds another layer of possibility to that of Grell I.

Ronsen, on the other hand, describes the preparation of an amorphous form of a completely different drug, paroxetine HCl, by vacuum or spray drying. Critically, the paroxetine HCl is provided as a paroxetine HCl/ethanol composition, see col. 2, lines 11-16, consistent with Bernstein's teaching that amorphous drugs can prepared by desolvation of a solvate. As with Bernstein, this adds nothing but more possibility to the teachings of Grell I.

In addition, even assuming Grell I disclosed evaporation (i.e., desolvation) of a (S)-repaglinide solvate or hydrate (which it does not), Doelker, *Ann. Pharm. Fr.*, 60:161-176 (2002) ("Doelker"), cited as supporting Rejection (D) in the Examiner's Answer, describes on pages 29-33 of the English translation the preparation of various solid state forms, including crystalline forms, by desolvation. Thus, according to Doelker, although amorphous pharmaceutical material may be obtained by desolvation, it is not true that amorphous products necessarily result from desolvation. This is insufficient to support a rejection based upon anticipation by inherency.

Accordingly, Appellants maintain that claims 38 and 40-48 are not anticipated by Grell I under § 102 (b), and the rejection should not be sustained.

B. Rejection of Claims 1, 34 and 35 Under 35 U.S.C. § 102(b)

Claims 1, 34 and 35 stand finally rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Grell I. Claims 1, 34 and 35 are directed to crystalline Form III of (S)-repaglinide. The Examiner stated in the Supplemental Examiner's Answer that reasonable evidence has been provided that the product as claimed is essentially the same as in Grell I (identified as Form A). Although Grell I did not identify whether the

solid form is the (S) form, were the Grell I form not the (S) form, a different infrared (“IR”) absorption spectrum would have been expected. Given the essentially same IR spectra, Appellants bear the burden of proof with reliable and reproducible factual evidence that the two forms are not the same. Appellants’ arguments about the differences in X-ray powder diffraction (“XRPD”) patterns were found unpersuasive by the Examiner because such data without correction and expert evaluation does not offer any rebuttal to the identity of the two products.

Appellants maintain that all the evidence of record indicates that the instant crystalline Form III of (S)-repaglinide and the Form A of Grell I are indeed different substances. The IR spectrum shown in Figure 3 of the instant specification was obtained with crystalline Form III of (S)-repaglinide (see page 17, ¶ 0055). In contrast, the IR spectrum shown in Figure 4 of Grell I was obtained with crystalline racemic repaglinide (see col. 32, lines. 15-68). Thus, regardless of any alleged similarities between the IR spectra, the fact remains that the instant Form III and Form A of Grell I are crystalline forms of different substances. The distinct natures of the instant crystalline Form III of (S)-repaglinide and Form A of racemic repaglinide of Grell I are confirmed by the difference in their melting points: 80-84°C for the instant Form III (see pages 25-27, ¶¶ 0079-0083), and 90-92°C for form A of Grell I, (see col. 32, lines 15-40).

Regarding the differences in XRPD patterns, Appellants noted in their Reply Brief that the XRPD data provided in Tables 1, 2 and 6 of the instant specification allows comparison of the instant crystalline Form III of (S)-repaglinide, not with Form A of racemic repaglinide of Grell I, but rather more fittingly with crystalline Forms I and II of (S)-repaglinide as prepared according to Example 3 of Grell I (see col. 85, line 40 to column 86, line 50). Applicants maintain that, notwithstanding the Examiner’s citation to U.S. Pharmacopia #23 and Davidovich et al., *Am. Phar. Rev.* 7:10, 12, 14, 100 (2004) (“Davidovich”) (which is not even prior art to the instant application) in the Examiner’s Answer, the XRPD data clearly demonstrate that the instant crystalline Form III of (S)-repaglinide and the crystalline Forms I and II of (S)-repaglinide prepared in Grell I are indeed different substances.

Appellants submit that the large differences in XRPD patterns are simply not the type of minor variation contemplated by Davidovich and U.S. Pharmacopia #23 as being due to artifacts, rather than true polymorphism, and that expert evaluation is not needed in this case to demonstrate a lack of identity. This is confirmed by the significant differences in the respective melting points of crystalline Form III of (S)-repaglinide and Forms I and II of (S)-repaglinide of Grell I: 80-84°C for instant Form III (see pages 25-27, ¶¶ 0079-0083), and 130-131°C for Form I (high-melting form) and 99-101°C for Form II (low-melting form) of Grell I (see col. 85, line 40, to col. 86, line 11).

Accordingly, Appellants maintain that claims 1, 34 and 35 are not anticipated by Grell I under § 102(b), and the rejection should not be sustained.

C. Rejection of Claims 1, 2, 4-37, 50, 51, 53, 54, 56 and 57 Under 35 U.S.C. § 103(a)

Claims 1, 2, 4-37, 50, 51, 53, 54, 56 and 57 stand finally rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Grell I in view of Grell II and Brittain. Claims 1, 2 and 4-37 are directed to crystalline Form III of (S)-repaglinide and a process for its preparation. Claims 50, 51, 53, 54, 56 and 57 are directed to a process for preparing crystalline Form II of (S)-repaglinide. The Examiner stated that a new polymorphic form is an obvious variation of the crystalline compound. Just because no one has spent the time and money trying out every solvent to identify every polymorphic form does not offer any unexpectancy of the polymorphic form. Such forms, upon spending more time and money, are expected to increase in number. According to the Examiner, Appellants have offered no explanation why giving the polymorph the name "Form III" provides any indicia of unobviousness.

Appellants have never asserted that the name "Form III" makes the claimed polymorph unobvious. Rather, it is a polymorph's unknown and unexpected properties that make it unobvious. See *In re Papesch*, 315 F.2d 381, 391 (CCPA 1963) (a chemical compound and its properties are inseparable). Appellants have repeatedly shown that the physical properties of Form III of (S)-repaglinide, such as its XRPD pattern and melting point, are distinct from those of the (S)-repaglinide forms disclosed in Grell I and Grell II. Appellants maintain that the proper test for obviousness in this

case is not whether the existence of (S)-repaglinide polymorphs is suggested by the prior art, but whether it would have been obvious to make the particular (S)-repaglinide form claimed, with all its properties, based on the prior art:

The law of § 103 requires quite a different inquiry from that conducted by the ALJ. The correct inquiry is not whether the Bouzard monohydrate [polymorph] could have been produced by manipulation of other cefadroxil processes, once the existence of the Bouzard monohydrate was known. The question is whether it would have been obvious to make the Bouzard monohydrate, based on the prior art.

Bristol-Myers Co. v. U.S. Int'l Trade Comm'n, 892 F.2d 1050, (Fed. Cir. Dec. 8, 1989) (unpublished decision) (emphasis added).

Here, the references cited by the Examiner suggest at most the possibility of other (S)-repaglinide polymorphs. The Examiner has still pointed to nothing in the cited references that would suggest to one skilled in the art the crystalline Form III of (S)-repaglinide recited in claims 1, 2, 4-37, or a method for its preparation.

The Board has previously dealt with similar situations. See *Ex parte Andrews*, Appeal No. 2002-0941 (BPAI 2003) (“[T]he examiner has not adequately explained how a person having ordinary skill would have been led from ‘here to there,’ i.e., from the [prior art] compound having formula I to the crystalline polymorph form I recited in claims 1 through 5.”); *Ex parte Portmann*, Appeal No. 2003-1199 (BPAI 2003) (same).

Similarly, the Examiner has still pointed to nothing in the cited references that would suggest to one skilled in the art the process for preparing crystalline Form II of (S)-repaglinide recited in claims 50, 51, 53, 54, 56 and 57, or a reasonable likelihood of success. See *Ex parte Gala*, Appeal No. 2001-0987 (BPAI 2001) (“Applicants have discovered specific solvents and experimental conditions, producing a distinctly different polymorph form 2 loratidine . . . This information stems from applicants’ specification, but not from the cited prior art”).

Accordingly, Appellants maintain that claims 1, 2, 4-37, 50, 51, 53, 54, 56 and 57 are not *prima facie* obvious over Grell I in view of Grell II and Brittain under § 103(a), and the rejection should not be sustained.

D. Rejection of Claims 8-18 Under 35 U.S.C. § 112, First Paragraph

Claims 8-18 stand finally rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Claims 8-18 are directed to a composition comprising crystalline Form III of (S)-repaglinide. The Examiner stated that it is very confusing as to what the claims represent when a limitation “requiring crystalline form III be maintained” is not present in the claims. Regarding Appellants’ argument that the instant specification clearly describes and enables methods for identifying and monitoring the crystalline form in the claimed compositions before, during and after their preparation, and that any composition lacking detectable Form III is simply outside the scope of claims 8-18, the examiner stated that this does not offer any factual support that the instant Form III would be spontaneously maintained, while others might need to invest tremendous effort, time and money for such endeavor.

Appellants maintain that the instant specification contains sufficient guidance to allow one of ordinary skill in the art to practice the invention of claims 8-18 without undue experimentation. Analysis, such as by X-ray diffraction, is quite common for a pharmaceutical company and can be relatively inexpensive. The Examiner’s concern that Form III may not be maintained or determined only with great difficulty is simply misplaced. As MPEP 2164.01(b) states:

Naturally, for unstable and transitory chemical intermediates, the “how to make” requirement does not require that the applicant teach how to make the claimed product in stable, permanent or isolatable form. *In re Breslow*, 616 F.2d 516, 521, 205 USPQ 221, 226 (CCPA 1980).

Here, the specification contains sufficient guidance to allow one of ordinary skill in the art to identify and monitor the crystalline form in the claimed compositions before, during and after their preparation without undue experimentation (see, e.g., page 16, ¶¶ 0053-0054; page 18, ¶ 0057). Thus, the specification teaches the skilled artisan how to make and use a composition comprising crystalline Form III of (S)-repaglinide. That is all that is required to satisfy the enablement requirement. Again, any composition lacking detectable Form III would simply be outside the scope of claims 8-18.

Accordingly, Appellants maintain that no case for lack of written description or enablement of claims 8-18 under § 112, first paragraph, has been made out, and the rejection should not be sustained.

CONCLUSION

Appellants submit that appealed claims 1-2, 4-38, 40-48, 50, 51, 53, 54, 56 and 57 meet all of the requirements for patentability under 35 U.S.C. §§ 102, 103 and 112. Accordingly, reversal of the Examiner's rejections is appropriate and is respectfully solicited.

Respectfully submitted,

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